PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Non-adherence to immunosuppressants following renal transplantation: A protocol for a systematic review
AUTHORS	Hucker, Abigail; Bunn, Frances; Carpenter, Lewis; Lawrence, Christopher; Farrington, Ken; Sharma, Shivani

VERSION 1 - REVIEW

REVIEWER	Dr Martin Howell School of Public Health, University of Sydney, Australia
REVIEW RETURNED	02-Mar-2017

GENERAL COMMENTS	General comment. Proposed review is of an important topic and an update of current knowledge would be useful. However, whether this update will advance the development of effective interventions is less clear to me. In my view the focus of the review should be on risk factors and clinical significance of non-adherence and should include all age groups as the period of transition from adolescent to young adult is known to be a time of high risk and should be a focus of interventions. The comments below are meant to improve the focus and clarify areas that were unclear to me. Specific comments. 1. Paragraph one – is not really needed. Focus should be on background to adherence – could just state that transplant is the preferred treatment for ESKD. 2. Similarly start of paragraph two is simplistic and unnecessary. Focus on what is known and why the need for the review, consequences etc. 3. Page 5 last paragraph. Should give reference to these reviews. Should also check the accuracy of the statement. For example reference [5] is a review published in 2005 and reference [22] was conducted in 2010. 4. Page 6 4th bullet point. Psychosocial factors including depression are important causes of non-adherence which is perhaps more relevant to the question. This may be the intent, however it is unclear. 5. Suggest that the review should aim to identify factors associated with or predictive of non-adherence i.e. determinants, in addition to or rather than barriers and facilitators. 6. The review would be more useful if it included children and adolescents given the issues of transition from adolescent to young adult and the high risk of non-adherence in this group. 7. Secondary outcomes should include risk factors for non-adherence as addressed in the studies. For example this may include age, time since transplant, comorbidities etc. Not clear what facilitators and barriers would be reported. This would seem to be more relevant to qualitative studies.

	8. Include PsycINFO database. 9. The search strategy provides little detail and does not include MESH terms and would be difficult to reproduce. Suggest authors review search strategies used in relevant Cochrane reviews and structure a search strategy accordingly. 10. Ideally should not exclude studies not written in English. The number of studies should at least be noted. 11. Data extraction – not sure why graft function should be singled out particularly as it is unlikely to be reported in the studies. Should be clarified. 12. The authors should refer to the Equator Network for reporting guidelines as these may provide better indicators of reporting quality and risk of bias than ref [23]. For example the STROBE statement. 13. Data synthesis should include a comparison of measurement methods e.g. self-report vs. more direct methods. Not clear that this will be done - it is important to know as self report is easier and cheaper and the extent of bias if any is useful to know for future studies as well as interpreting current studies. 14. It is not clear how the review will address barriers and facilitators? Rather it may identify key risk factors.

REVIEWER	Demetra Tsapepas NewYork-Presbyterian Hospital
REVIEW RETURNED	06-Mar-2017

GENERAL COMMENTS	This is an interesting paper summarizing the importance of adherence following solid organ transplantation. Authors nicely summarize methodology that can be used to identify papers but do not provide guidance on interpretation or summary of the results and impactful recommendations. This methodology paper needs to take a further step in synthesis rather than explain methods. The literature on this topic is sufficient for such an approach.

REVIEWER	Norberto Perico IRCCS - Mario Negri Institute for Pharmacological Research, Italy
REVIEW RETURNED	04-Apr-2017

GENERAL COMMENTS	Hucker and colleagues presented the protocol of a systematic review and meta-analysis aimed to summarize available literature regarding non-adherence to immunosuppressive therapy in adult kidney allograft recipients. This information could eventually guide interventions to improve medication compliance in the clinical transplant setting. The Authors may wish to consider the following drawbacks: 1. The Introduction is aimed to address risk factors for non-adherence in kidney transplantation. However, it is quite confusing since the concept that younger age, being unmarried and perceiving low social support are determinants of poor adherence to immunosuppressive treatment in renal transplant recipients has been reported twice (Page 5, lines 3-4; Page 5, lines 9-10). Such repetition should be avoided. Moreover, it is worth mentioning that a prerequisite for optimal medication adherence is access to therapy. Indeed, cost-related non-adherence to immunosuppressive drugs has been documented among kidney transplant recipients (Clin J

	Am Soc Nephrol 2010; 5:2323; N Eng J Med 2012; 366:586). 2. One of the aims of the present review and meta-analysis is to estimate the impact of non-adherence on psychological correlates, such as depression or anxiety and illness perception (Page 6, lines 13-14). However, psychological distress, in particular depression, is a risk factor for and not a consequence of non-adherence to immunosuppressive therapy in kidney transplant recipients. This aim should be reformulated accordingly. 3. In the Methods and design section the Authors stated that a second reviewer will independently screen 25% of the titles, abstracts and full texts for quality assurance (Page 8, lines 7-9). However, based on the same protocol registered on the PROSPERO database (registration number: CRD42016038751), a second reviewer will independently screen 15% of the titles, abstracts and full texts. Similarly, it was stated that one reviewer will independently rate for quality assurance 25% of the studies chosen at random (Page 9, lines 15-17), whereas according to the protocol registered on the PROSPERO database the corresponding percentage is 15%. It should be clarify whether these are typing errors or the Authors decided to increase the proportion of studies controlled in order to guarantee quality. 4. The paragraph related to Data synthesis is unclear. In particular, it was stated that risk ratios/odds ratios (with 95% confidence intervals) and hazard ratios will be presented using meta-analysis to pool effect estimated for period prevalence, point prevalence and survival outcomes (Page 9, lines 19-21). However, it seems unlikely that period prevalence and point prevalence could be expressed as risk ratios/odd ratios or hazard ratios. This information needs to be checked. Furthermore, the description of the above analyses should be reported after indicating that meta-analysis will be included in this review if there is sufficient homogeneity across outcomes and available data. 5. According to the protocol registered on the PROSPERO database, subgroup analyses could be performed whereas in the present manuscript there is no indication about these analyses. Actually, it would be valuable to assess adherence to immunosuppressive medications after stratifications for factors known to affect compliance, such as age, ethnicity and socio-economic status, provided that there is enough homogeneity across outcomes and available data. Minor points: – In the Methods and analysis section of the Abstract the last sentence can be removed (Page 2, lines 16-17) because the aims of the meta-analysis have already been reported in the previous sentences. – Regarding the toxicity of immunosuppressive medications (Page 4, lines 17-19), it should be outlined that some adverse events are ascribed to immunosuppression itself (enhanced risk of opportunistic infections and selected malignancies) while other are unrelated to immunosuppression (e.g., nephrotoxicity of calcineurin inhibitors, hypertension and cardiovascular disease resulting from use of corticosteroids). – As for reference #14 (Transplant Proc 2003; 35:2868), the first Author of the study is Jindal RM and not Jindel RM.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

1. Paragraph one – is not really needed. Focus should be on background to adherence – could just state that transplant is the preferred treatment for ESKD.
The first paragraph has been shortened and re-focused. The information that remains is that which the author's feel is useful for providing a clear background to the patient population.

2. Similarly start of paragraph two is simplistic and unnecessary. Focus on what is known and why the need for the review, consequences etc.
The second paragraph has been shortened. We have, however, retained some of the information that is useful for providing a clear understanding about why non-adherence may occur, such as the high burden of medication taking and unpleasant side effects experienced.

3. Page 5 last paragraph. Should give reference to these reviews. Should also check the accuracy of the statement. For example reference [5] is a review published in 2005 and reference [22] was conducted in 2010.
Actioned – references have been included where suggested. Accuracy of the statement has also been checked – the review publishing years have been correctly reported.

4. Page 6 4th bullet point. Psychosocial factors including depression are important causes of non-adherence which is perhaps more relevant to the question. This may be the intent, however it is unclear.
Actioned – phrasing of aim has been changed to address this point.

5. Suggest that the review should aim to identify factors associated with or predictive of non-adherence i.e. determinants, in addition to or rather than barriers and facilitators.
Actioned – as suggested, phrasing has been changed from "barriers and facilitators" to "factors associated with".

6. The review would be more useful if it included children and adolescents given the issues of transition from adolescent to young adult and the high risk of non-adherence in this group.
We agree that transition is a pertinent issue. However, it is not within the scope of the current protocol to include children and adolescents. This is guided by evidence that different challenges lead to non-adherence in this group compared to adults. For example, see an existing review, published in 2010 (reference 22 in manuscript) conducted in pediatric kidney transplant patients. We feel that transition in itself would require a dedicated review as opposed to being a sub component of the proposed protocol. As this research is being conducted as part of a PhD, it is also outside of our available resources to include this patient population to allow full consideration of the existing evidence.

7. Secondary outcomes should include risk factors for non-adherence as addressed in the studies. For example this may include age, time since transplant, comorbidities etc. Not clear what facilitators and barriers would be reported. This would seem to be more relevant to qualitative studies.
Actioned - as suggested, phrasing has been changed from "barriers and facilitators" to "factors associated with".

8. Include PsycINFO database.
The University of Hertfordshire does not have access to the PsycINFO database. Instead, we have access to SCOPUS, which captures most of the same literature as PsycINFO. This database will be used in the review.

9. The search strategy provides little detail and does not include MESH terms and would be difficult to

reproduce. Suggest authors review search strategies used in relevant Cochrane reviews and structure a search strategy accordingly.
Actioned – as suggested, the search strategy has been amended to include a combination of free-text and MeSH search terms. A draft of the search strategy to be used in PubMed is included in table 1.

10. Ideally should not exclude studies not written in English. The number of studies should at least be noted.
Ideally, we would include studies not written in English, however, unfortunately, we do not have the resources to translate such content and will acknowledge this limitation in any forthcoming manuscripts resulting from the research.

11. Data extraction – not sure why graft function should be singled out particularly as it is unlikely to be reported in the studies. Should be clarified.
Actioned – this has been removed.

12. The authors should refer to the Equator Network for reporting guidelines as these may provide better indicators of reporting quality and risk of bias than ref [23]. For example the STROBE statement.
In our view, it is not appropriate to use the STROBE statement, as the STROBE statement is for the reporting of primary studies, rather than a quality assessment tool. The Down's and Black is an assessment tool for non-randomised studies – we will omit any questions that will not be appropriate for this review etc. An existing published review (Carpenter et al., 2016) has also successfully used the modified Down's and Black quality assessment tool. However, this highlights an important area that needs addressing, as there is currently no set quality checklist for this purpose.

- Carpenter L, Nikiphorou E, Sharpe R, et al. Have radiographic progression rates in early rheumatoid arthritis changed? A systematic review and meta-analysis of long-term cohorts. Rheumatology 2016;55:1053-1065.

13. Data synthesis should include a comparison of measurement methods e.g. self-report vs. more direct methods. Not clear that this will be done - it is important to know as self report is easier and cheaper and the extent of bias if any is useful to know for future studies as well as interpreting current studies.
Thank you for the suggestion. Actioned - we have included this in the data extraction but needed to additionally include in the data synthesis section also. This has now been added, where we have indicated that we would do the following: discuss the potential to do a stratified analysis or meta-regression to compare measurement methods, dependent on the number of categories and number of studies within each category.

14. It is not clear how the review will address barriers and facilitators? Rather it may identify key risk factors.
Actioned – as suggested, phrasing has been changed from "barriers and facilitators" to "factors associated with".

Reviewer: 2

This is an interesting paper summarizing the importance of adherence following solid organ transplantation. Authors nicely summarize methodology that can be used to identify papers but do not provide guidance on interpretation or summary of the results and impactful recommendations. This methodology paper needs to take a further step in synthesis rather than explain methods. The literature on this topic is sufficient for such an approach.
Thank you for the suggestion. As this is a protocol, the manuscript summarises how the systematic

review will be conducted. As the systematic review has not yet been completed, there are currently no results to summarise. Once completed, the systematic review and meta-analysis will be submitted for publication, where a summary of the results and impactful recommendations will be included.

Reviewer: 3

1. The Introduction is aimed to address risk factors for non-adherence in kidney transplantation. However, it is quite confusing since the concept that younger age, being unmarried and perceiving low social support are determinants of poor adherence to immunosuppressive treatment in renal transplant recipients has been reported twice (Page 5, lines 3-4; Page 5, lines 9-10). Such repetition should be avoided.
Actioned – as suggested, the section containing repetition has been deleted.
Moreover, it is worth mentioning that a prerequisite for optimal medication adherence is access to therapy. Indeed, cost-related non-adherence to immunosuppressive drugs has been documented among kidney transplant recipients (Clin J Am Soc Nephrol 2010; 5:2323; N Eng J Med 2012; 366:586).
Actioned – this suggestion has been considered and included at the end of the first paragraph on page 5, to highlight that non-adherence to immunosuppressive medication could be cost-related, as documented in previous research exploring insurance coverage in U.S. renal transplant recipients. Suggested reference has also been cited.

2. One of the aims of the present review and meta-analysis is to estimate the impact of non-adherence on psychological correlates, such as depression or anxiety and illness perception (Page 6, lines 13-14). However, psychological distress, in particular depression, is a risk factor for and not a consequence of non-adherence to immunosuppressive therapy in kidney transplant recipients. This aim should be reformulated accordingly.
Actioned - phrasing of aim has been changed to address this point.

3. In the Methods and design section the Authors stated that a second reviewer will independently screen 25% of the titles, abstracts and full texts for quality assurance (Page 8, lines 7-9). However, based on the same protocol registered on the PROSPERO database (registration number: CRD42016038751), a second reviewer will independently screen 15% of the titles, abstracts and full texts. Similarly, it was stated that one reviewer will independently rate for quality assurance 25% of the studies chosen at random (Page 9, lines 15-17), whereas according to the protocol registered on the PROSPERO database the corresponding percentage is 15%. It should be clarify whether these are typing errors or the Authors decided to increase the proportion of studies controlled in order to guarantee quality.
Actioned - The authors decided to increase the proportion of studies that are independently screened for added quality assurance. The PROSPERO database has now been updated to match the numbers reported in this protocol.

4. The paragraph related to Data synthesis is unclear. In particular, it was stated that risk ratios/odds ratios (with 95% confidence intervals) and hazard ratios will be presented using meta-analysis to pool effect estimated for period prevalence, point prevalence and survival outcomes (Page 9, lines 19-21). However, it seems unlikely that period prevalence and point prevalence could be expressed as risk ratios/odd ratios or hazard ratios. This information needs to be checked. Furthermore, the description of the above analyses should be reported after indicating that meta-analysis will be included in this review if there is sufficient homogeneity across outcomes and available data.
Actioned – the information has been checked and the section re-phrased appropriately to address this review point. In addition, the data synthesis section has been re-organised to report the summary of the meta-analysis after indicating that meta-analysis will be included in this review if there is sufficient homogeneity across outcomes and if data are available.

5. According to the protocol registered on the PROSPERO database, subgroup analyses could be performed whereas in the present manuscript there is no indication about these analyses. Actually, it would be valuable to assess adherence to immunosuppressive medications after stratifications for factors known to affect compliance, such as age, ethnicity and socio-economic status, provided that there is enough homogeneity across outcomes and available data.
Actioned – the data synthesis section has been updated to mention the inclusion of sub-group analyses between studies in the meta-analyses, provided that there is sufficient homogeneity across outcomes and available data.

Minor points:
– In the Methods and analysis section of the Abstract the last sentence can be removed (Page 2, lines 16-17) because the aims of the meta-analysis have already been reported in the previous sentences.
Actioned – this has been removed as suggested.
– Regarding the toxicity of immunosuppressive medications (Page 4, lines 17-19), it should be outlined that some adverse events are ascribed to immunosuppression itself (enhanced risk of opportunistic infections and selected malignancies) while other are unrelated to immunosuppression (e.g., nephrotoxicity of calcineurin inhibitors, hypertension and cardiovascular disease resulting from use of corticosteroids).
Actioned – this suggestion has been considered and included in the second paragraph of the introduction following the list of side effects that are ascribed to immunosuppression itself, to highlight that patients may also experience adverse events that are unrelated to immunosuppression.
– As for reference #14 (Transplant Proc 2003; 35:2868), the first Author of the study is Jindal RM and not Jindel RM.
Actioned – the author surname spelling has been corrected.

VERSION 2 – REVIEW

REVIEWER	Martin Howell School of Public Health University of Sydney Australia
REVIEW RETURNED	23-May-2017

GENERAL COMMENTS	I am satisfied that the authors have addressed my review comments and look forward to the reading the review when it is published.

REVIEWER	Norberto Perico IRCCS Mario Negri Institute for Pharmacological Research, Italy
REVIEW RETURNED	23-May-2017

GENERAL COMMENTS	In the revised version the Authors added the required information. However, some imprecision needs to be corrected: 1. It was stated that two core reviews published in 2003 and 2004 aimed to highlight the extent of non-adherence to immunosuppressive medications in kidney transplant recipients (Page 5, lines 31-32; Page 6, line 1 of the revised version with changes highlighted in bold). However, the quoted reviews were published in 2012 and 2003, respectively. Proper reference(s) should be provided.